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Monographs on drugs which are frequently analyzed in therapeutic drug monitoring

Rentsch, K ; Buhl, Daniela ; Eap, Chin Bin ; Fathi, Marc ; Jöchle, Wolfgang ; Magnin, Jean-Luc ;
Thormann, Wolfgang ; Werner, Dominique

Abstract: In addition to the monographs which have been published in the past 4 years by the working group "Drug Monitoring" of the Swiss Society of Clinical Chemistry (SSCC) [1-4], new monographs have been written. The data presented in these monographs provide an overview of important information for the request and interpretation of results. Therefore, laboratory health professionals and the receivers of the reports are the targeted readers. In this series, several antiepileptic drugs are presented. Monographs on carbamazepine [1], lamotrigine [2], phenobarbital [2], and valproic acid [2] have been published previously. First, information about pharmacology and pharmacokinetics of these drugs (protein binding, metabolic pathways and enzymes involved, elimination half-life time and elimination route(s) of the parent drug and therapeutic as well as toxic concentrations) is given. Second, the indications for therapeutic drug monitoring are listed. Last but not least, important pre-analytical information is provided, including time points of blood sampling and time interval after which steady-state concentrations are reached after changing the dose. Furthermore, the stability of the drug and its metabolite(s) after blood sampling is described. For readers with a specific interest, references to important publications are given. The number of the monographs will be further enlarged. The updated files are presented on the homepage of the SSCC (www.sccc.ch). We hope that these monographs are helpful for the better handling of therapeutic drug monitoring and we are looking forward to comments from the readers

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Other titles: Arzneimittel-Monographien für Medikamente, die regelmäßig im Rahmen des Therapeutic Drug Monitorings analysiert werden

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Monographs on drugs which are frequently analyzed in therapeutic drug monitoring

Arzneimittel-Monographien für Medikamente, die regelmäßig im Rahmen des Therapeutic Drug Monitorings analysiert werden

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Abstract

In addition to the monographs which have been published in the past 4 years by the working group “Drug Monitoring” of the Swiss Society of Clinical Chemistry (SSCC) [1–4], new monographs have been written. The data presented in these monographs provide an overview of important information for the request and interpretation of results. Therefore, laboratory health professionals and the receivers of the reports are the targeted readers. In this series, several anti-epileptic drugs are presented. Monographs on carbamazepine [1], lamotrigine [2], phenobarbital [2], and valproic acid [2] have been published previously. First, information about pharmacology and pharmacokinetics of these drugs (protein binding, metabolic pathways and enzymes involved, elimination half-life time and elimination route(s) of the parent drug and therapeutic as well as toxic concentrations) is given. Second, the indications for therapeutic drug monitoring are listed. Last but not least, important pre-analytical information is provided, including time points of blood sampling and time interval after which steady-state concentrations are reached after changing the dose. Furthermore, the stability of the drug and its metabolite(s) after blood sampling is described. For readers with a specific interest, references to important publications are given. The number of the monographs will be further enlarged. The updated files

are presented on the homepage of the SSCC (www.sccc.ch). We hope that these monographs are helpful for the better handling of therapeutic drug monitoring and we are looking forward to comments from the readers.

Keywords: antiepileptics; clonazepam; ethosuximide; gabapentine; levetiracetam; oxcarbazepine; phenytoin; primidone; topiramate; vigabatrin.

Zusammenfassung

Ergänzend zu den in den letzten vier Jahren publizierten Arzneimittelmonographien der Arbeitsgruppe „Medikamente“ der Schweizerischen Gesellschaft für Klinische Chemie (SGKC) [1–4], sind weitere Monographien erstellt worden. Der Labormediziner bzw. der Empfänger der Befunde soll mit diesen Monographien eine Übersicht über die wichtigsten Informationen erhalten, die für die Veranlassung einer Analyse bzw. für die Interpretation der Resultate hilfreich sind. In dieser Serie werden verschiedene Antiepileptika präsentiert. Die Monographien zu Carbamazepin [1], Lamotrigin [2], Phenobarbital [2], und Valproinsäure [2] wurden bereits in früheren Serien publiziert. Die einzelnen Monographien beinhalten einerseits Angaben zu klinisch-pharmakologischen Daten, wie zum Beispiel zu den Proteinbindungen, Metabolisierungswegen und daran beteiligten Enzymen, Halbwertszeiten und Eliminationswege der Muttersubstanz sowie Informationen zu therapeutischen bzw. toxischen Bereichen. Andererseits werden bei jeder Substanz die Indikationen für das Therapeutic-Drug-Monitoring aufgelistet und wichtige Angaben zur Präanalytik gemacht (Zeitpunkt der Blutentnahme und Zeitpunkt des Erreichens einer Steady-state-Situation nach einer Dosisänderung). Außerdem werden Angaben über die Stabilität der Medikamente bzw. ihrer Metaboliten nach der Blutentnahme gemacht. Für die interessierten Leser sind die verwendeten Referenzen als Zitate aufgeführt. Die Zahl der Monographien wird fortlaufend ergänzt. Die aktuellsten Versionen der Monographien sind auf der Homepage der SGKC abrufbar (www.sccc.ch). Wir hoffen, dass diese Monographien im Umgang mit dem Therapeutic-Drug-Monitoring hilfreich sein werden und freuen uns über Kommentare und Bemerkungen.

Schlüsselwörter: Antiepileptika; Clonazepam; Ethosuximid; Gabapentin; Levetiracetam; Oxcarbazepin; Phenytoin; Primidon; Topiramat; Vigabatrin.

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Clonazepam

General

- Class of the drug: Antiepileptics
- Synonym(s):
- Common trade name(s) in Germany: Rivotril®
- Conversion factors: $\mu\text{g/L} \times 3.167 = \text{nmol/L}$
 $\text{nmol/L} \times 0.316 = \mu\text{g/L}$

Clinical pharmacology

- Indications for TDM: Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
- Protein binding: 85%
- Elimination half-life: 20–60 h
- Volume of distribution: 3 L/kg
- Metabolism:
 - Main metabolic pathways: CYP3A4
 - Active metabolite(s)? 7-amino-clonazepam
 - Inhibitor or inducer of the cytochrome P450 system? No
 - Other significant pharmacokinetic interactions: None
- Elimination of parent drug: Hepatic
- Typical therapeutic range: 20–40 $\mu\text{g/L}$ (63–127 nmol/L)
- Potentially toxic concentration: > 100 $\mu\text{g/L}$ (> 316 nmol/L)

Pre-analytics

- Time to steady-state since beginning of treatment or change of posology: ~4–10 days
- Time for blood sampling: Before next dose at steady-state
- Type(s) of sample: Serum or plasma
- Stability: 1 week at 4°C

Remarks

None

References

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- Walson PD, Edge JH. Clonazepam disposition in pediatric patients. *Ther Drug Monit* 1996;18:1–5.
- Baumann PB, Hiemke C, Ulrich S, Eckermann G, Gaertner I, Gerlach M, et al. The AGNP-TDM expert group consensus guidelines: therapeutic drug monitoring in psychiatry. *Pharmacopsychiatry* 2004;37:246–65.

Ethosuximide

General

- Class of the drug: Antiepileptics
- Synonym(s):
- Common trade name(s) in Germany: Petnidan[®], Suxilep[®]
- Conversion factors: $\text{mg/L} \times 7.082 = \mu\text{mol/L}$
 $\mu\text{mol/L} \times 0.141 = \text{mg/L}$

Clinical pharmacology

- Indications for TDM: Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
- Protein binding: No
- Elimination half-life: 48–60 h
- Volume of distribution: 0.7 L/kg
- Metabolism:
 - Main metabolic pathways: CYP3A
 - Active metabolite(s)? No
 - Inhibitor or inducer of the cytochrome P450 system? No
 - Other significant pharmacokinetic interactions: None
- Elimination of parent drug: Mainly hepatic, 20% renal
- Typical therapeutic range: 40–100 mg/L (280–700 $\mu\text{mol/L}$)
- Potentially toxic concentration: > 141 mg/L (> 1000 $\mu\text{mol/L}$)

Pre-analytics

- Time to steady-state since beginning of treatment or change of posology: ~7–10 days
- Time for blood sampling: Before next dose at steady-state
- Type(s) of sample: Serum or plasma
- Stability: 1 week at 4°C

Remarks

None

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Gabapentine

General

- Class of the drug: Antiepileptics
- Synonym(s):
- Common trade name(s) in Germany: Neurontin®
- Conversion factors: $\text{mg/L} \times 5.840 = \mu\text{mol/L}$
 $\mu\text{mol/L} \times 0.171 = \text{mg/L}$

Clinical pharmacology

- Indications for TDM: Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
- Protein binding: No
- Elimination half-life: 5–15 h
- Volume of distribution: 58 L/kg
- Metabolism:
 - Main metabolic pathways: No metabolites identified
 - Active metabolite(s)? No
 - Inhibitor or inducer of the cytochrome P450 system? No
 - Other significant pharmacokinetic interactions: None
- Elimination of parent drug: Renal
- Typical therapeutic range: 1.7–20.5 mg/L (10–120 $\mu\text{mol/L}$)
- Potentially toxic concentration: Not known

Pre-analytics

- Time to steady-state since beginning of treatment or change of posology: ~ 30 h
- Time for blood sampling: Before next dose at steady-state
- Type(s) of sample: Serum or plasma
- Stability: 1 week at 4°C

Remarks

Nonlinear kinetics of absorption

References

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- Gauthier D, Gupta R. Determination of gabapentin in plasma by liquid chromatography with fluorescence detection after solid-phase extraction with a C18 column. Clin Chem 2002;48:2259–61.

Levetiracetam

General

- Class of the drug: Antiepileptics
- Synonym(s):
- Common trade name(s) in Germany: Keppra®
- Conversion factors: $\text{mg/L} \times 5.875 = \mu\text{mol/L}$
 $\mu\text{mol/L} \times 0.1702 = \text{mg/L}$

Clinical pharmacology

- Indications for TDM: Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
- Protein binding: < 10%
- Elimination half-life: 6–8 h
- Volume of distribution: 0.5–0.7 L/kg
- Metabolism:
 - Main metabolic pathways: Enzymatic hydrolysis in blood
 - Active metabolite(s)? No
 - Inhibitor or inducer of the cytochrome P450 system? No
 - Other significant pharmacokinetic interactions: None
- Elimination of parent drug: Renal
- Typical therapeutic range: 5–30 mg/L (29.4–176 $\mu\text{mol/L}$)
- Potentially toxic concentration: > 400 mg/L (> 2350 $\mu\text{mol/L}$)

Pre-analytics

- Time to steady-state since beginning of treatment or change of posology: ~ 2 days
- Time for blood sampling: Before next dose at steady-state
- Type(s) of sample: Serum or plasma
- Stability: 1 week at 4°C

Remarks

None

References

- Arzneimittelkompendium Schweiz. Basel: Documed, 2009.
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Oxcarbazepine

General

• Class of the drug:	Antiepileptics
• Synonym(s):	
• Common trade name(s) in Germany:	Trileptal [®] , Apydan [®] , Timox [®]
• Conversion factors:	Oxcarbazepine: $\text{mg/L} \times 4.0 = \mu\text{mol/L}$ $\mu\text{mol/L} \times 0.252 = \text{mg/L}$ Monohydroxy-oxcarbazepine (MHD): $\text{mg/L} \times 3.94 = \mu\text{mol/L}$ $\mu\text{mol/L} \times 0.254 = \text{mg/L}$

Clinical pharmacology

• Indications for TDM:	Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
• Protein binding:	MHD: 40% (albumin)
• Elimination half-life:	Oxcarbazepine: 1–3 h MHD: 11–15 h
• Volume of distribution:	Oxcarbazepine: 3–15 L/kg MHD: 0.7 L/kg
• Metabolism:	
– Main metabolic pathways:	Hydroxylation
– Active metabolite(s)?	Yes (MHD)
– Inhibitor or inductor of the cytochrome P450 system?	Inhibitor of CYP2C19; inductor of CYP3A4
– Other significant pharmacokinetic interactions:	None
• Elimination of parent drug:	Oxcarbazepine: mainly hepatic MHD: mainly renal
• Typical therapeutic range:	Oxcarbazepine: 0.025–0.33 mg/L (0.1–1.3 $\mu\text{mol/L}$) MHD: 7.6–20.3 mg/L (30–80 $\mu\text{mol/L}$)
• Potentially toxic concentration:	Not known

Pre-analytics

• Time to steady-state since beginning of treatment or change of posology:	~ 2 days
• Time for blood sampling:	Before next dose at steady-state
• Type(s) of sample:	Serum or plasma
• Stability:	1 week at 4°C

Remarks

None

References

- Arzneimittelkompendium Schweiz. Basel: Documed, 2009.
- Schulz M, Schmoldt A. Therapeutic and toxic blood concentrations of more than 800 drugs and other xenobiotics. Pharmazie 2003;58:447–74.
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Phenytoin

General

- Class of the drug: Antiepileptics
- Synonym(s): Diphenylhydantoin
- Common trade name(s) in Germany: Zentropil[®], Phenhydan[®]
- Conversion factors: $\text{mg/L} \times 3.96 = \mu\text{mol/L}$
 $\mu\text{mol/L} \times 0.252 = \text{mg/L}$

Clinical pharmacology

- Indications for TDM: Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
- Protein binding: 90% (albumin)
- Elimination half-life: 20–60 h (concentration-dependent; increases at higher levels due to saturation of metabolism)
- Volume of distribution: 0.5–0.8 L/kg
- Metabolism:
 - Main metabolic pathways: Hydroxylation by CYP2C9 and CYP2C19 (main metabolite: p-hydroxy-diphenylhydantoin) followed by glucuroconjugation
 - Active metabolite(s)? No
 - Inhibitor or inducer of the cytochrome P450 system? Inductor of cytochromes CYP2C9, CYP2C19, and CYP3A4/5
 - Other significant pharmacokinetic interactions: Numerous other interactions
- Elimination of parent drug: Mainly hepatic
- Typical therapeutic range: 10–20 mg/L (40–80 $\mu\text{mol/L}$)
- Potentially toxic concentration: > 20 mg/L (> 80 $\mu\text{mol/L}$)

Pre-analytics

- Time to steady-state since beginning of treatment or change of posology: 5–14 days (concentration-dependent)
- Time for blood sampling: Before next dose at steady-state
- Type(s) of sample: Serum or plasma
- Stability: 48 h at 4°C

Remarks

A small increase of the dose might produce a disproportional increase in plasma concentration due to the nonlinear kinetics of phenytoin.
In case of hypoalbuminemia or diminished binding, the free fraction of phenytoin increases.
Slow hydroxylators could develop toxic effects at a common posology.

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Primidone

General

• Class of the drug:	Antiepileptics
• Synonym(s):	
• Common trade name(s) in Germany:	Mylepsinum®
• Conversion factors:	Primidone: $\text{mg/L} \times 4.58 = \mu\text{mol/L}$ $\mu\text{mol/L} \times 0.218 = \text{mg/L}$ Phenobarbital: $\text{mg/L} \times 4.31 = \mu\text{mol/L}$ $\mu\text{mol/L} \times 0.232 = \text{mg/L}$

Clinical pharmacology

• Indications for TDM:	Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
• Protein binding:	<20%
• Elimination half-life:	Primidone: 5–16 h Phenobarbital: 50–150 h Phenylethylmalonamide: 16–50 h
Volume of distribution:	0.6 L/kg
Metabolism:	
– Main metabolic pathways:	CYP2C9 and CYP2C19
– Active metabolite(s)?	Phenobarbital Phenylethylmalonamide
– Inhibitor or inducer of the cytochrome P450 system?	Inductor of cytochromes CYP2C9, CYP2C19, and CYP3A4
– Other significant pharmacokinetic interactions:	Numerous interactions, e.g., with other antiepileptics, oral anticoagulants, steroids
• Elimination of parent drug:	Hepatic: 17%–73% Renal: 15%–65%
• Typical therapeutic range:	Primidone: 5–12 mg/L (23–55 $\mu\text{mol/L}$) Phenobarbital: 15–40 mg/L (64–172 $\mu\text{mol/L}$)
• Potentially toxic concentration:	Primidone: > 15 mg/L (> 69 $\mu\text{mol/L}$)

Pre-analytics

• Time to steady-state since beginning of treatment or change of posology:	Primidone: 2 days Phenobarbital: 10–30 days
• Time for blood sampling:	Before next dose at steady-state
• Type(s) of sample:	Serum or plasma
• Stability:	48 h at 4°C

Remarks

TDM of primidone must include measurement of its main active metabolite phenobarbital

References

- Arzneimittelkompendium Schweiz. Basel: Documed, 2009.
- Schweizerische Gesellschaft für Klinische Pharmakologie und Toxikologie, Grundlagen der Arzneimitteltherapie (16. Auflage). Basel: Documed, 2005.
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- Warner A, Privitera M, Bates D. Standards of laboratory practice: antiepileptic drug monitoring. National Academy of Clinical Biochemistry. Clin Chem 1998;44:1085–95.

Topiramate

General

- Class of the drug: Antiepileptics
- Synonym(s):
- Common trade name(s) in Germany: Topamax[®], Topiramat-Jansen[®]
- Conversion factors:
 $\text{mg/L} \times 4.23 = \mu\text{mol/L}$
 $\mu\text{mol/L} \times 0.236 = \text{mg/L}$

Clinical pharmacology

- Indications for TDM: Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
- Protein binding: 13%–17%
- Elimination half-life: 21 h
- Volume of distribution: 0.55–0.8 L/kg (lower in women than in men)
- Metabolism:
 - Main metabolic pathways: Not known
 - Active metabolite(s)? No
 - Inhibitor or inducer of the cytochrome P450 system? Strong inducer of CYP3A4, strong inhibitor of CYP2C19
 - Other significant pharmacokinetic interactions: Not known
- Elimination of parent drug: Mainly renal, hepatic 20% (50% if treated with other antiepileptics)
- Typical therapeutic range: 4.0–12.2 mg/L (16.9–51.6 $\mu\text{mol/L}$)
- Potentially toxic concentration: Not known

Pre-analytics

- Time to steady-state since beginning of treatment or change of posology: 4–5 days
- Time for blood sampling: Before next dose at steady-state
- Type(s) of sample: Serum or plasma
- Stability: 1 week at 4°C

Remarks

None

References

- Arzneimittelkompendium Schweiz. Basel: Documed, 2009.
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Vigabatrin

General

- Class of the drug: Antiepileptics
- Synonym(s): Gamma-vinyl GABA
- Common trade name(s) in Germany: Sabril®
- Conversion factors: $\text{mg/L} \times 7.7 = \mu\text{mol/L}$
 $\mu\text{mol/L} \times 0.130 = \text{mg/L}$

Clinical pharmacology

- Indications for TDM: Verification of compliance
- Protein binding: No
- Elimination half-life: 5–8 h (elderly 12–13 h)
- Volume of distribution: 1.0–1.4 L/kg
- Metabolism:
 - Main metabolic pathways: No metabolites identified
 - Active metabolite(s)? No
 - Inhibitor or inducer of the cytochrome P450 system? No
 - Other significant pharmacokinetic interactions: A gradual reduction of approximately 20%–30% in plasma phenytoin concentration has been observed following add-on therapy with vigabatrin
- Elimination of parent drug: Mainly renal
- Typical therapeutic range: No direct correlation between concentration and effectiveness. Because vigabatrin acts irreversibly, it would be unlikely to have a therapeutic range
- Potentially toxic concentration: Not known

Pre-analytics

- Time to steady-state since beginning of treatment or change of posology: 2 days
- Time for blood sampling: Before next dose at steady-state
- Type(s) of sample: Serum or plasma
- Stability: 1 week at 4°C

Remarks

S-enantiomer pharmacologically active
Irreversible enzyme inhibition (GABA transaminase); half-life of the drug is clinically not relevant

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3. Rentsch K, Eap CB, Fathi M, Grignaschi N, Magnin JL, Thormann W, et al. Monographs on drugs which are frequently analysed in therapeutic drug monitoring. *J Lab Med* 2008;32:372–81.
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